

The control of heart rate: the physiology of the sinoatrial node and the role of the I_f current

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A heart will beat approximately 25×10^8 times during the course of a human being's life. The observation that most mammals share the same number of heart beats per lifetime, be it a mouse (600 bpm for 2 years) or a giant tortoise (6 bpm for 200 years), has led people to suggest that if we slowed our heart rate we might live longer! While there may not be a causal relationship in fit healthy animals, there is an impressive literature accumulating suggesting that there is a clear and strong association between a lower heart rate and improved prognosis in a variety of diseases. It is, of course, in cardiovascular disease where the slowing of heart rate with specific bradycardic agents may offer the most advantage. The question as to whether I_f inhibition can specifically improve morbidity and life expectancy in cardiovascular disease is one we only recently have had the tools to answer, and the introduction of ivabradine into the armamentarium offers a unique opportunity to address this question. We will know a lot more when the BEAUTIFUL trial (MorBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) concludes in December 2007.

*We are all born with a finite number of heart beats:
I, for one, am not going to waste mine on exercise*

*Dr A. Glenn Morrow
(attributed by Dr J. Borer)*

A fundamental feature of the mammalian heart is its ability to maintain rhythmic contractions in the absence of external stimulation. The mammalian heart contains a myogenic, or muscle-derived, pacemaker, the sinoatrial node (SA)—a small, but complex, conglomeration of specialized tissue located in the outer reaches of the right atrium. The impulses arising from the pacemaker both determine the heart rate and provide a target for its physiological and pharmacological modulation. The node contains a mixture of nodal cells, connective tissue and atrial cells, and an understanding of the complex interplay between these tissues is essential for understanding how the node works. The specialized nodal cells are themselves not homogeneous—cells from the center of the node being both morphologically and electrophysiologically different from more peripheral cells. However, the defining feature of the nodal cells themselves is that they show inherent pacemaker activity—that is, their diastolic membrane potential is not stable, but gradually depolarizes to a threshold from which a new action potential is triggered. The ionic currents present during this pacemaker depolarization

Keywords: sinoatrial node; heart rate; pacemaker; ion current; action potential; HCN channel; ivabradine

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SELECTED ABBREVIATIONS AND ACRONYMS

BEAUTIFUL	MorBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction
HCN	hyperpolarization-activated cyclic nucleotide-gated cation channel
SA	sinoatrial (node)

phase are many (at least 10 have been identified) and this provides levels of redundancy to the function of the node that make it very hard to stop. Nodal cells also have one other significant feature—they do not have the large time-independent background potassium current (I_{K1}) that is present in ventricular cells. This gives the nodal cell a high-input impedance, which, in short, means small currents can exert big effects! Perhaps one of the most important of these small currents is the hyperpolarization-activated inward current— I_f . I_f is the target for adrenergic and cholinergic modulation of heart rate: agents that increase I_f accelerate heart rate and those that inhibit I_f slow heart rate. This article reviews the physiology of the SA node and, in particular, the importance of I_f in the regulation of heart rate. Understanding the physiology of the SA node allows the understanding of how such a small current can exert a significant effect on heart rate and the seemingly contradictory observation that even complete blockade of this current is safe and will only slow heart rate by about 30%.

EXTRINSIC VS INTRINSIC PACEMAKERS

What can we learn from evolution?

As evolution progressed from simple single cells to complex multicellular organisms with discrete specialized tissues, the need for an efficient circulatory system developed in parallel. Simple invertebrates such as the brachiopods (clam-like shellfish) and ascidians (sea squirts) circulate rudimentary blood-like substances around open body cavities aided by inefficient peristaltic "tube" hearts.¹ Higher invertebrates such as the decapods (lobsters) and the cephalopods (octopi, etc) evolved more complex multichambered hearts that require synchronization, coordination, and rhythm (for review see reference 1). To generate the rhythm, nature experimented with two different strategies: (i) *extrinsic* neuronally derived pacemakers; or (ii) *intrinsic* specialized muscle tissue. The intrinsic *myogenic* pacemakers are actually both evolutionarily ancient and widespread—being present in most molluscs, insects, and all vertebrates (apart from the lamprey). Myogenic hearts have their own intrinsic muscle-derived pacemaker, continue to beat when isolated, and contract sequentially with the wave of contraction spreading monotonically from one point to another. Neurogenic hearts are found in the annelids (segmented worms), crustaceans, and arachnids (spiders), receive their pacemaker commands from an *extra*-cardiac source (the cardiac ganglion), stop when isolated, and all

parts of the heart tend to contract simultaneously. Both neurogenic and myogenic pacemakers have their advantages and disadvantages. Neurogenic hearts provide instant control, but are easy to stop. The simultaneous contraction of a neurogenic heart works well in a tube heart, but poorly in a multichambered heart. Myogenic pacemakers, conversely, are very hard to stop, but require complex and slow regulation via circulating factors from both endocrine and paracrine sources. The wave-like propagation of contraction in the myogenic heart has mechanical advantages for a single chamber, but does not easily allow for synchronization and coordination between chambers.

While the mammalian pacemaker is essentially myogenic, rather than choosing between these two evolutionary blueprints, the mammalian heart has incorporated the best features of both systems.

The pacemaker of the mammalian heart: a functional mix?

The primary pacemaker of the mammalian heart is the SA node, which consists of specialized myocardial tissue (ie, is "myogenic") (see Boyett et al² for review). Excitation spreads from the node via the atrial muscle before arriving at the atrioventricular node. Here the impulse is first delayed and then moved rapidly through the specialized "neuronal-like" conduction pathways ("neurogenic") of the bundle of His and Purkinje fiber system before spreading in a propagated wave ("myogenic") through the myocardium from apex to base. In this way, the mammalian pacemaker generates a robust myocardially derived pacemaker, its more organized or "neuronal-like" propagation allows for the necessary coordination of contraction of a multichambered heart, and, within chambers, the contraction wave favors ejection by spreading toward the outflow tracts of the respective chambers.

LOCATION AND STRUCTURE OF THE MAMMALIAN SINOATRIAL NODE

Gross anatomy

The SA node is a small tear-drop shaped cluster of specialized tissue located in the right atrium at the junction of the superior vena cava, the inferior vena cava and, the crista terminalis (*Figure 1*).³ In man, estimates of the size of the node vary from 7 to 20 mm in length^{4,5} and, in the rabbit, 2 to 4 mm in diameter × 6 to 8 mm in length.³ The mammalian SA node is a heterogeneous mixture of specialized nodal cells (which

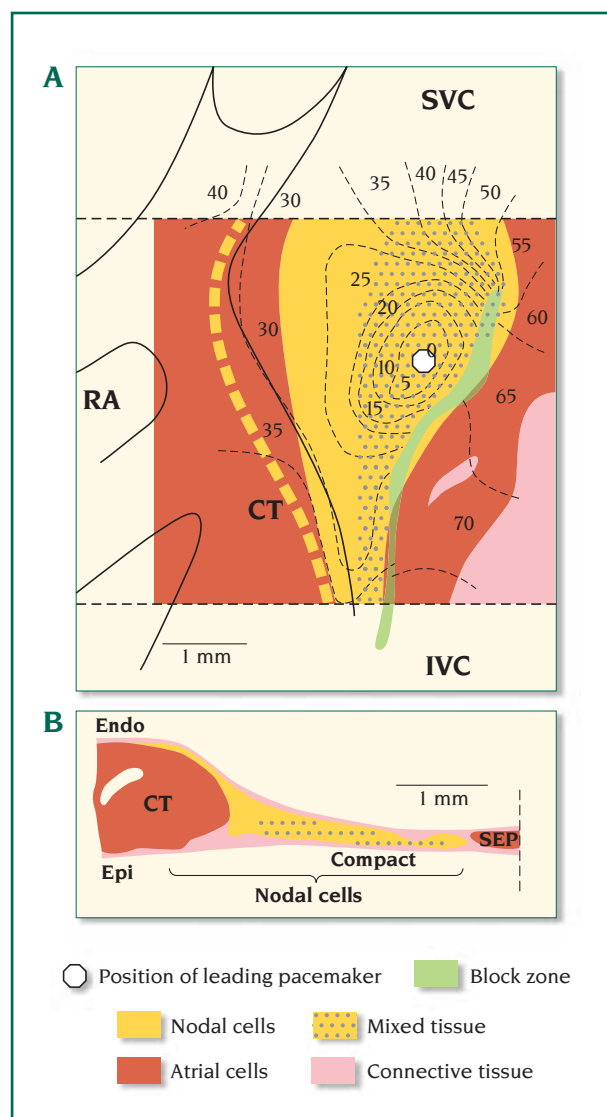


Figure 1. Diagram showing the major tissue types and anatomy of the rabbit SA node when viewed from the endocardial surface (A) and in cross-section (B). The various tissue types are color-coded as indicated. The dashed yellow line shows the extent of the nodal tissue underlying the atrial tissue. The dark dotted lines show isochrones at the times indicated (in ms) for the propagation of an impulse away from the leading pacemaker site.

Abbreviations: CT, crista terminalis; Epi, epicardium. Endo, endocardium; IVC inferior vena cava; RA, right atrial appendage; SA, sinoatrial (node); SEP, interatrial septum; SVC, superior vena cava.

Redrawn from reference 3: Bleeker WK, Mackaay AJ, Masson-Pevet M, Bouman LN, Becker AE. Functional and morphological organization of the rabbit sinus node. *Circ Res.* 1980;46:11-22. Copyright © 1980, Lippincott Williams & Wilkins.

around and down towards the atrioventricular node.² Figure 1 also shows a region of low conductance (the block zone), which is located close to the leading pacemaker site and provides a region of conduction block preventing excitation from spreading prematurely towards the septum. This anatomical arrangement and the circuitous "up and around" excitation exit pathway from the node may confer physiological advantages by: (i) ensuring the wave of atrial contraction spreads from the very top of the chamber forcing blood down towards the atrioventricular valve; and (ii) the block zone may then prevent reentry of electrical excitation from the atrium back into the node.

Microanatomy

The specialized nodal tissue is itself heterogeneous (Figure 2, next page).^{3,7} Close to the center of the node, the cells are small (5 to 10 μm in diameter and 25 to 30 μm long), spindle-shaped, poorly differentiated, contain few myofilaments or mitochondria, and have highly convoluted membranes containing many caveolae (Figure 2A). In short, central nodal cells (sometimes called P cells) are the site of the primary pacemaker. Moving outward away from the center of the node, in most species there is a gradual transition with cells becoming larger, having a clear myofilament structure, and containing more mitochondria (Figure 2B) the closer you get to the periphery of the node.^{2,3,7} Interspersed within the node are a third type of nodal cell termed "spider cells," which are seen when the node is disaggregated into its component parts (Figure 2).⁷ The role of these spider cells is uncertain, but clearly their extensive "dendritic" structure and their large surface-volume ratio may suit them to influence the propagation of the electrical wave within the microdomains of the node and to facilitate electrical coupling between adjacent areas.

are themselves by no means homogeneous), atrial myocytes and a surprisingly large amount of connective tissue (Figure 1). The amount of connective tissue within the node varies with species⁴ and age,⁶ but can make up between 50% and 90% of the node. It is now clear that both the preponderance of connective tissue and the mixture of other excitable tissues within the SA node are fundamentally important to normal function.²

The location of the leading pacemaker site in the rabbit SA node is shown in Figure 1 and the isochrones show the propagation of the wave of excitation away from its site of initiation.² Contrary to the schematics in most textbooks, the wave of excitation actually spreads anteriorly and obliquely (towards the top left of Figure 1) towards the crista terminalis, which it meets as a broad wave front before turning and heading

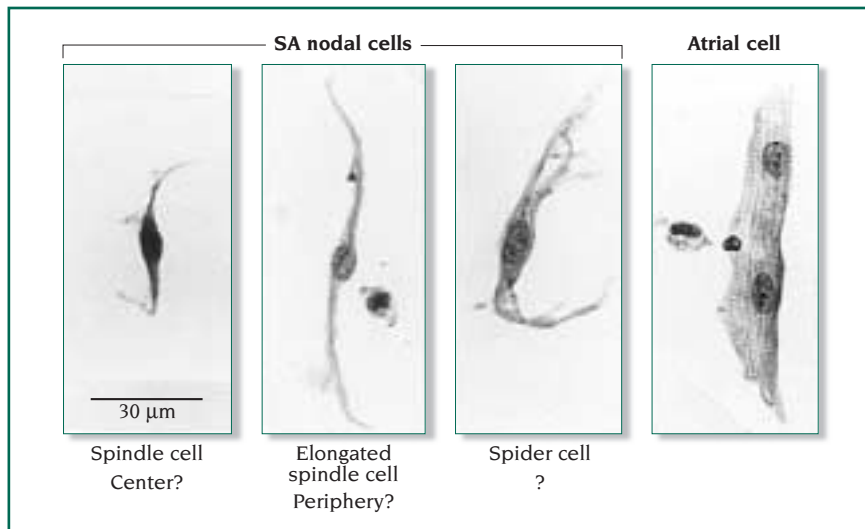


Figure 2. Photomicrographs of the four different cell types isolated from the rabbit sinoatrial (SA) node. Cells are stained with hematoxylin and eosin.

Reproduced from reference 7: Verheijck EE, Wessels A, van Ginneken AC, et al. Distribution of atrial and nodal cells within the rabbit sinoatrial node: models of sinoatrial transition. *Circulation*. 1998;97:1623-1631. Copyright © 1998, Lippincott Williams & Wilkins.

CELLULAR ELECTROPHYSIOLOGY OF SINGLE NODAL CELLS

Regional differences within the node

The vast majority of cells within the node show the slow diastolic pacemaker depolarization phase that is the defining characteristic of the SA nodal action potential (Figure 3A) and provides the fundamental requisite "clock function." However, the exact shape of the action potential varies among the differing cell types within the node reflecting an underlying heterogeneity of ion channel expression across the node.^{2,8} The small cells, presumed to be from the center of the node, have lower resting membrane potentials and a slower diastolic depolarization phase than the larger peripheral cells.⁸ The smaller cells also have a slow action potential upstroke, reflecting a low expression of Na channels and a depolarization phase dominated by Ca inward current. In moving away from the center of the node towards the periphery, the expression of Na channels increases and with this comes a faster, taller action potential.⁸ Isolated peripheral nodal cells also show an increase in their spontaneous beating rate (above that seen in situ) and an increased rate of diastolic depolarization—most likely as a consequence of an increase in the pacemaker current I_f .^{9,10}

Figure 3. Spontaneous action potentials recorded from two cells isolated from rabbit sinoatrial (SA) node. A: recording from a small cell (22pF) assumed to be from the center of the node. B: recording from a large cell (57.5pF) assumed to be from the periphery of the node.

Reproduced from reference 8: Honjo H, Boyett MR, Kodama I, Toyama J. Correlation between electrical activity and the size of rabbit sino-atrial node cells. *J Physiol*. 1996;463:795-808. Copyright © 1996, Cambridge University Press.

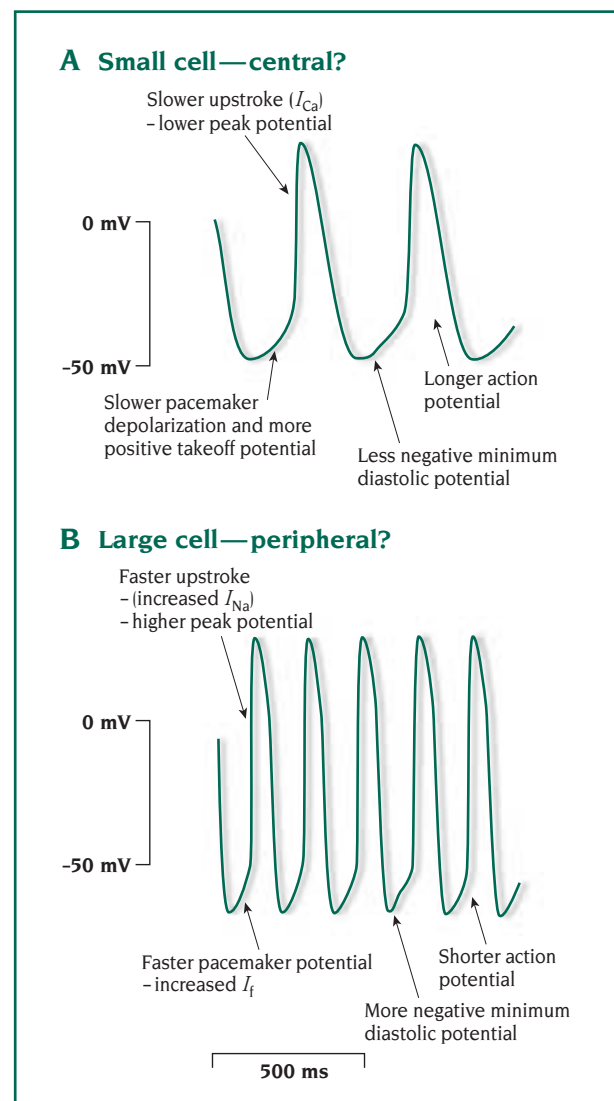




Figure 4. Principal ionic currents responsible for pacemaker activity in the sinoatrial node. These currents were calculated using the Oxsoft Heart model (v4.0). To allow comparison, all currents are plotted using the same vertical scale and hence the peak of the L-type calcium current is off-scale at around -470 pA. The T-type Ca current is small in this model and is not shown. In addition, the current generated by the electrogenic Na/K pump is also not shown.

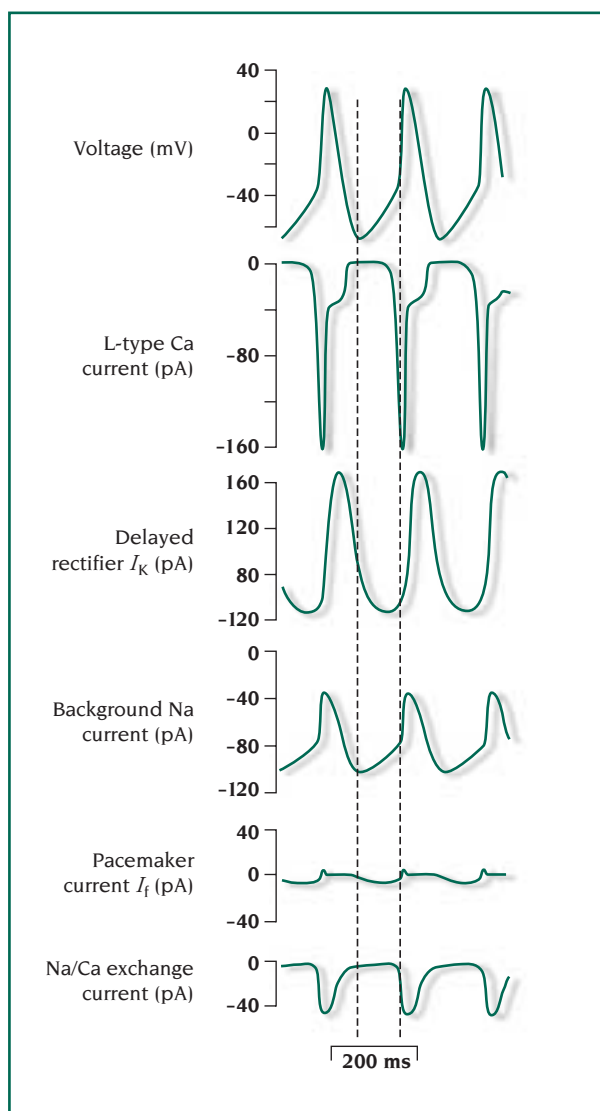
This increase in firing rate of the peripheral tissue is probably a feature of isolated cells as, in the intact heart, the electrotonic coupling of these cells to the surrounding atrial tissue is likely to counteract this effect.²

The heterogeneous distribution of ion channel expression in the various regions of the node allows the primary pacemaker site to "wander" according to prevailing conditions.² Activation or inhibition of a particular channel thus does not inhibit the node altogether, but simply allows the primary pacemaker site to shift to a region of the node where these channels play a more minor role.² This spatial heterogeneity is thus a key safety feature of the node making it very hard to stop.

Multiple currents make the node both hard to stop and exquisitely regulatable

Not only does the spatial heterogeneity of ion channel expression provide a fail-safe pacemaker, but *within* individual cells the multiple ionic currents underlying pacemaker activity provide layers of redundancy. *Figure 4* shows a computer simulation (Oxsoft Heart v 4.0) of the principal ion currents underlying the SA node action potential. For comparison, these currents have all been plotted on the same vertical scale. At least 10 ionic currents have now been identified as contributing to the SA node action potential.^{11,12} However, Irisawa et al (1993) have pointed out only two currents are required to produce rhythmic activity in nodal cells—a time-independent outward current and the Ca inward current (I_{Ca}).¹³ Thus, the multiple ionic currents within nodal cells provide levels of redundancy that again make the node hard to stop—a very useful safety feature.

Figure 4 also shows another key feature of the node: that is, currents known to exert a substantial effect on rate (such as the pacemaker current I_f) may only be quite small under physiological conditions. While the role of I_f in pacemaker function has been extensively debated and investigated,^{14,15} it is clear that the selective blockade of this small current can undoubtedly modulate rate *in vivo* (see below and Borer et al¹⁶). Thus, not only do the multiple ion currents of the SA



node provide a fail-safe mechanism they also provide for exquisite regulation, as small currents (or small changes in large currents) can fundamentally influence SA node rate.

How can small currents have such a big effect on heart rate?

In ventricular cells, the resting membrane potential is determined principally by the high permeability of the membrane to potassium ions and the intra- and extracellular potassium concentrations. Thus, in ventricular myocytes, the resting membrane potential (ie, where net current flow is zero) is typically around -85 mV. The relationship between current flow and voltage is described by Ohm's Law (Voltage = Current \times Resistance; or $V=IR$). *Figure 5A* (next page) shows this rela-

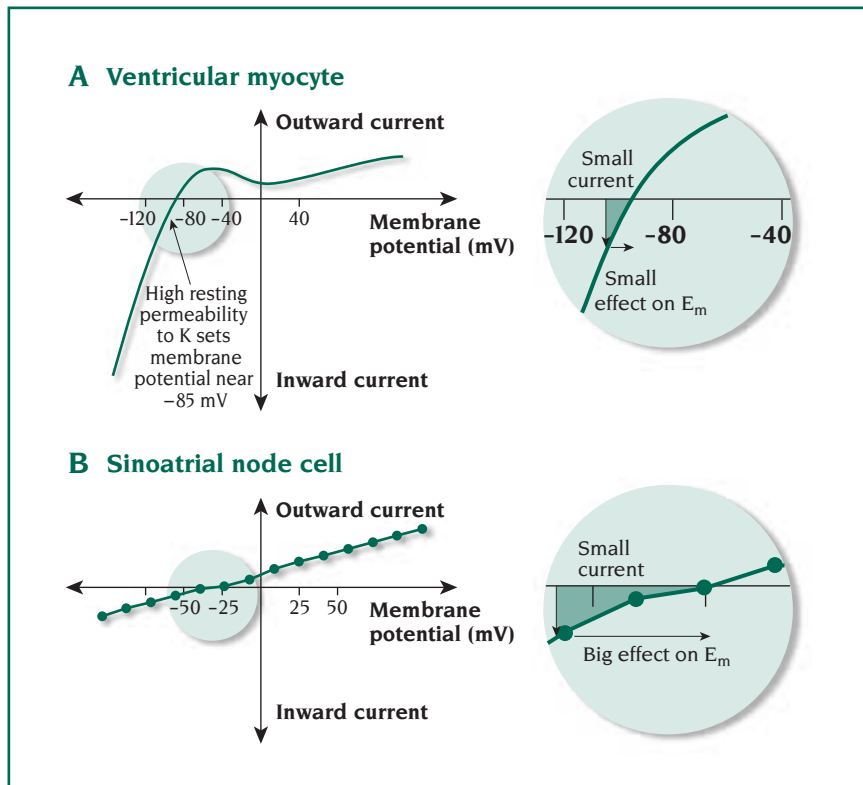


Figure 5. Illustration of the differences in current-voltage (I - V) relationships for the steady-state background current in ventricular myocytes and sinoatrial (SA) nodal cells. **A:** representation of the steady-state I - V relationship for I_{K1} in ventricular cells showing it intersecting the voltage axis at the resting membrane potential. The K^+ conductance of the resting membrane is high (ie, the slope of the I - V relationship is steep) such that a small current exerts only a small effect on membrane potential (see inset). **B:** shows the lack of I_{K1} in the SA node cell gives a shallow steady-state I - V relationship (ie, low conductance, high impedance) and hence a small current can induce a large change in membrane voltage (see inset).

The data in **B** are redrawn from reference 17: Noma A, Nakayama T, Kurachi Y, Irisawa H. Resting K conductances in pacemaker and non-pacemaker heart cells of the rabbit. *Jpn J Physiol.* 1984;34:245-254. Copyright © 1984, Center for Academic Publications Japan.

relationship for the resting membrane of a ventricular myocyte, and this steady-state current through potassium channels is carried by the inward rectifier— I_{K1} . This current-voltage relationship crosses the voltage axis at the resting membrane potential (ie, around -85 mV) and, because the membrane is very permeable to potassium at these voltages, the slope of this relationship is steep (ie, conductance is high). Thus, at around -85 mV, where the "resistance" of the membrane is low, a small current has only a small effect on membrane voltage (*Figure 5A inset*). This makes the resting potential of a ventricular cell inherently stable and protects the cell against inappropriate excitability and arrhythmias—a useful feature for ventricular cells. Contrast this with the situation in a SA node cell (*Figure 5B*). The *input impedance* (resistance) of the SA node cell is ≈ 30 times that of a ventricular myocyte^{17,18} (ie, the slope of the I - V relationship is much shallower). SA node cells lack the inward rectifier current (I_{K1}) that provides the high K permeability to resting ventricular cells. A small change in current in an SA node cell can thus result in a large change in membrane potential (*Figure 5B inset*). Thus, the membrane potential of SA node cells is, by design, inherently unstable and very small changes in current can profoundly influence the shape of the action potential. The high-input impedance of SA node cells thus means that the

intrinsic rate of firing of the node is exquisitely regulatable through small modulations of the ion currents underlying the pacemaker depolarization.

THE "PACEMAKER CURRENT" I_f

Characteristics

In 1979, Brown and colleagues in Oxford identified an inward current in SA node preparations that had the unusual property of being activated on hyperpolarization of the cell membrane.¹⁹ At this time, a hyperpolarization-activated inward current was so unusual it was termed the "funny" current— I_f . Since then, a similar current carried, as it transpires, by the same family of channels, has been identified in neuronal and retina cells and has been termed the hyperpolarization-activated current I_h (see Pape²⁰ for review).

Figure 6 shows the principal property of I_f —that is, it is activated by hyperpolarizations negative to -50 mV. I_f can be carried by a mixture of Na and K ions (although Na is the major carrier in physiologic settings) and has all the features necessary to be a primary pacemaker current in the heart.^{21,22} For example, I_f : (i) is activated on hyperpolarization from a threshold of about -50 mV (and is fully activated around -110 mV)

and hence contributes to diastolic "pacemaker" depolarization; (ii) is increased by β -receptor stimulation; and (iii) is inhibited by acetylcholine (ACh).²¹

Role of I_f in the control of heart rate

While it is clear that I_f may influence pacemaker function, the extent to which it is important in the control of heart rate has been hotly debated.^{14,15,23,24} While DiFrancesco and colleagues^{14,25} have argued that I_f is exclusively responsible for pacemaker activity, others have suggested that it plays only a minor role.^{15,23,24,26} The roots of some of this controversy are illustrated in *Figure 6A*. The diastolic depolarization phase of the SA node action potential shows a maximum diastolic potential of -60 to -65 mV, which depolarizes gradually to about -55 mV over about 200 ms. From *Figure 6B*, however, it is clear that I_f is both slow to activate and

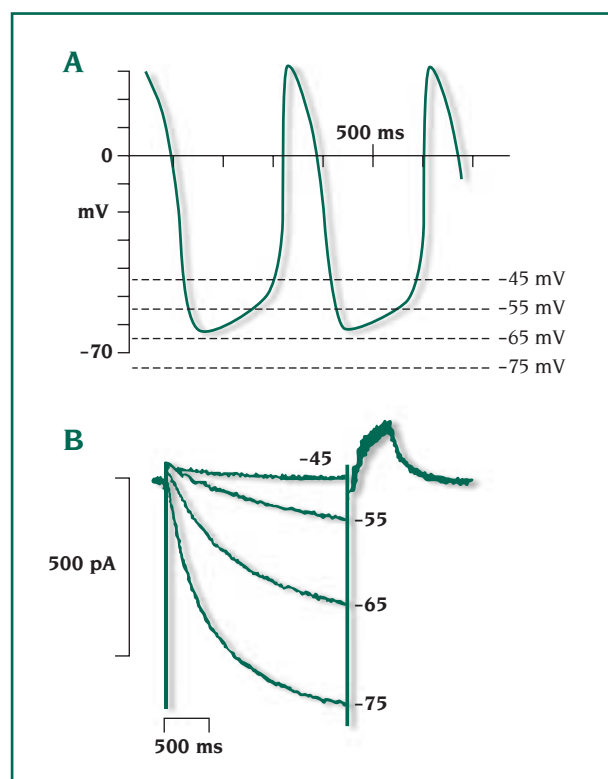


Figure 6. Spontaneous action potentials recorded from an isolated SA nodal cell (A) and the hyperpolarisation-activated (I_f) current recorded in response to voltage-clamp steps (B). The dotted lines in A indicate the voltages of the clamp-steps shown in B. This illustrates that, in this case, the diastolic depolarization phase of the action potential goes from around -60 mV to around -50 mV in about 150 ms. Note: the slow activation kinetics of the currents shown in panel B mean that, at these voltages, the activation of I_f is relatively small after 150 ms.

Redrawn from reference 22: Baruscotti M, DiFrancesco D. Pacemaker channels. *Ann N Y Acad Sci.* 2004;1015:111-121. Copyright © 2004, New York Academy of Sciences.

small at these voltages. Thus, 100 to 200 ms into the voltage-clamp steps shown in *Figure 6B*, at voltages between -65 and -55 mV, I_f will only reach about 40 pA at most. These observations, and others, have led to the suggestion that I_f does not play a major role in cardiac automaticity, but simply is there to prevent excessive hyperpolarization.^{2,15,23,24,26}

Much of the debate about I_f and its importance, or lack thereof, in pacemaking relates to the specific details and conditions under which in vitro experiments are performed.^{14,15} A simpler and pragmatic answer to the question, "Does I_f contribute to pacemaker function in man?" is provided by the clinical studies of agents reported to be specific and selective for I_f inhibition. For example, ivabradine (0.3 - 3 μ M) is a potent inhibitor of I_f ²⁷ and, at these concentrations, has been shown to reduce heart rate by 10 to 15 bpm in clinical studies.¹⁶ Since ivabradine has been shown to be selective for I_f at these concentrations,²⁷ this would suggest that I_f does indeed contribute to the control of heart rate in vivo. What is clear from this debate is that while I_f certainly contributes to pacemaker function, it is not the sole determinant of rhythmic activity. This again shows that there are levels of redundancy within the SA node that provide a fail-safe feature such that that cardiac rhythm can be both initiated and regulated in the event of the failure of any given mechanism.

Regulation of I_f

The firing rate of the SA node is exquisitely modulated by innervation from the autonomic nervous system. Basal heart rate is under the influence of a maintained vagal tone and sympathetic stimulation can dramatically increase heart rate. In isolated SA node cells, β -receptor stimulation increases, and ACh slows, the rate of SA node cell diastolic depolarization (*Figure 7A*, next page). The original description of I_f by Brown et al in 1979 showed that this current is substantially increased by β -receptor stimulation.¹⁹ *Figure 7B* shows a series of steady-state activation curves for I_f .²⁸ These curves describe the fraction of channels activated at a given potential and the control curve shows that at -60 mV only $\approx 23\%$ of available channels are activated. However, β -receptor stimulation shifts this activation curve to the right such that at -60 mV there is an 87% increase in available channels. Conversely, ACh shifts the activation curve to the left, reducing the available channels at -60 mV by 70%.

These shifts in the activation curve for I_f are mediated by changes in intracellular concentration of cAMP.

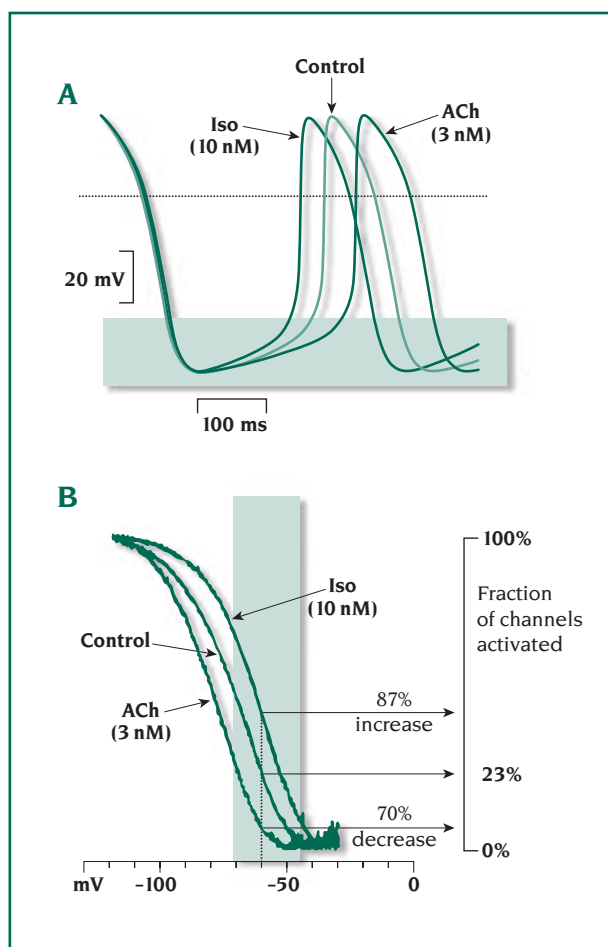


Figure 7. Effect of β -receptor and muscarinic-receptor stimulation on: (A) spontaneous action potentials recorded from an isolated sinoatrial (SA) nodal cell; and (B) the steady-state activation curve for I_f . Isoprenaline (Iso) accelerates, and acetylcholine (ACh) slows, the spontaneous rate of an isolated SA node cell by altering the rate of diastolic depolarization. The shaded area in both panels indicates the diastolic voltage range from -45 to -70 mV. Panel B shows that at -60 mV only 23% of the available channels are activated. However, the fraction of channels available increases by 87% in isoprenaline (10 nM) or decreases by 70% in response to ACh (3 nM).

Panel A is redrawn from reference 21: DiFrancesco D. Pacemaker mechanisms in cardiac tissue. *Annu Rev Physiol.* 1993;55:455-472. Copyright © 1993, Annual Reviews.

Panel B is redrawn from reference 28: Accili EA, Robinson RB, DiFrancesco D. Properties and modulation of I_f in newborn versus adult cardiac SA node. *Am J Physiol.* 1997;272(3 pt 2):H1549-1552. Copyright © 1997, American Physiological Society.

Molecular identity and tissue distribution of I_f channels

The channel responsible for the cardiac I_f current is now known to be a member of a family of channels termed the hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channels (for review see reference 22). Four HCN genes have been identified in mammalian tissues, termed HCN1-4. RNA messages for all 4 HCN isoforms have been found in heart,³⁴ but in the SA node HCN4 is the dominant isoform in most species, accounting for $\approx 80\%$ of the messages.³⁵⁻³⁷ In mouse, HCN2 makes up the remainder with only very low levels of HCN1.³⁷ This is not the case in rabbit where the remaining 20% is mostly HCN1.³⁶ HCN1 is highly expressed in retinal photoreceptors^{37,38} and in the brain.^{39,40} HCNs 2 and 3 are also expressed in brain.^{40,41}

Within the SA node the expression of HCN channels is not uniform. Cells from the center of the node show little I_f current, while towards the periphery I_f is larger,^{9,10} and this correlates with a heterogeneous expression of HCN4 channels.⁴²

Studies in knockout mice have shown that the homozygote deletion of the gene encoding HCN4 is embryologically lethal.⁴³ However, hearts and cardiomyocytes could still be isolated from these embryos and they showed I_f reduced by 80% and heart rate by about 40%. Importantly, the HCN4-deficient hearts still contracted regularly without arrhythmias, showing that, as suggested above, while I_f clearly contributes to pacemaker function, it is not the sole determinant of rhythmicity. Interestingly, the contraction rate in HCN4-deficient hearts was unaffected by raising cAMP, suggesting that this channel not only contributes significantly to basal heart rate, but also mediates the chronotropic response to adrenergic stimulation.⁴³

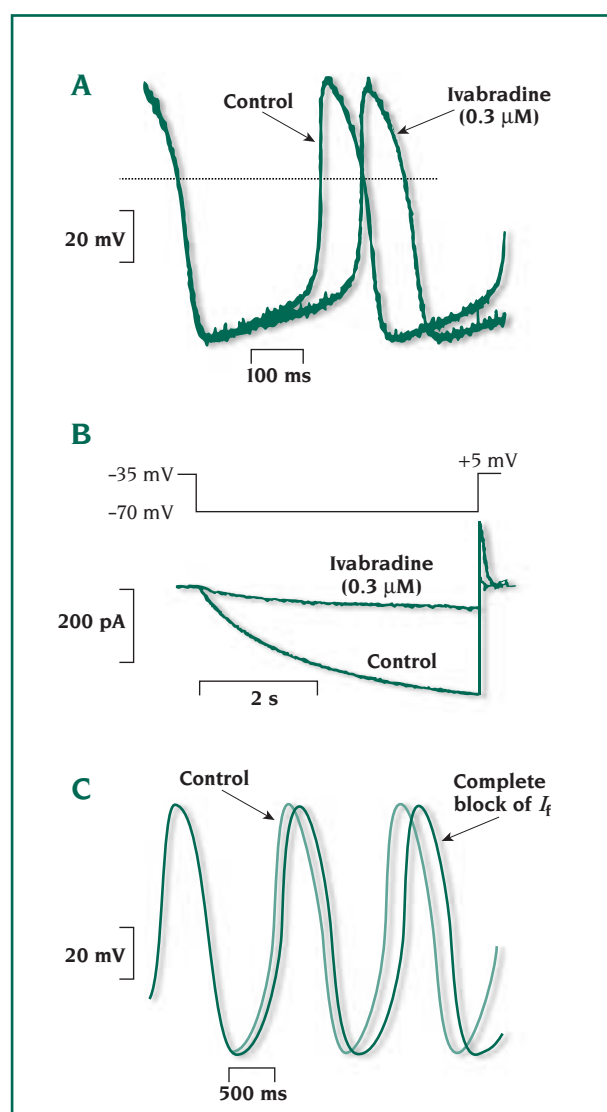
β -Receptor stimulation, through its activation of adenylyl cyclase, elevates cAMP, which then binds directly to the cytoplasmic tail of the I_f channel, shifting its activation curve to the right. Conversely, ACh, via muscarinic receptors, inhibits adenylyl cyclase, decreases cAMP, and shifts the I_f activation curve to the left. DiFrancesco and colleagues have argued that this is the explanation for the negative chronotropic effects of ACh in contrast to the established textbook explanation—that is, ACh activates an ACh-dependent K current ($I_{K,ACh}$).²⁹ In support of this, these authors have shown that low concentrations of ACh (0.01-0.03 μ M) inhibit I_f without affecting $I_{K,ACh}$, and an increase in $I_{K,ACh}$ requires 20 times the concentrations required to inhibit I_f .²⁹

In addition to the modulation of I_f by autonomic neurotransmitters, a number of other physiologically-relevant agents have been shown to modulate this current. Activators of I_f include vasoactive intestinal peptide (VIP),³⁰ thyroid hormone (T3),³¹ and nitric oxide,³² while I_f is inhibited by neuropeptide Y (NPY) and adenosine.³³



Consequences of I_f block

An elevated resting heart rate has been shown to correlate strongly with increased mortality in angina,⁴⁴ heart failure,⁴⁵ and even cancer.⁴⁶ While the literature suggests that heart rate represents an independent risk factor,^{46,47} it is possible that it is an epiphenomenological indicator of an underlying increase in sympathetic tone. In recent years the pharmaceutical industry has searched for pure bradycardic agents that can lower heart rate without the negative inotropic consequences of β -blockade or Ca antagonism.⁴⁸ The list of such specific bradycardic agents (SBAs) now includes alinidine, zatebradine, and ivabradine. *Figure 8A* shows that ivabradine ($0.3 \mu\text{M}$) slows the rate of diastolic depolarization in an SA node cell, and hence slows the firing rate of this cell (in this case by approximately



18%), *without* changing the shape of the subsequent action potential.²² The inhibitory action of ivabradine on I_f is shown in *Figure 8B* where a higher concentration ($3 \mu\text{M}$) reduces I_f by $\approx 78\%$. Ivabradine blocks the channel when it is in its open state and hence its block is use-dependent—that is, in isolated tissues its ability to block the channel increases as the beating rate increases.²⁷ While such use-dependence sounds an attractive feature (ie, the drug should exert a larger effect when heart rate is high) evidence from Borer et al¹⁶ (2003) suggests that in man the negative chronotropic effect of ivabradine in absolute terms is comparable at rest and during peak exercise.

Figure 8C shows a computer simulation (*Cellular Open Resource; COR* - Oxford University)⁴⁹ of the effects of the complete blockade of I_f on the SA node action potential. This model predicts that, under steady state conditions, complete blockade of I_f will reduce SA node rate by approximately 20% to 30% in an isolated cell. This demonstrates the fail-safe feature of SA node cells discussed earlier—that the intrinsic pacemaker activity of the node is not dependent on a single ionic current and hence intrinsic pacemaker activity at the level of a single cell or, when integrated across the entire node, is hard to stop.

Figure 9A (next page) shows the dose-response relationship for ivabradine in isolated SA node cells²⁷ with a half-maximal inhibitory concentration of $2.2 \mu\text{M}$. *Figure 9B* shows a dose-titration study in patients where the dose of ivabradine has been increased stepwise from 5 to 20 mg bid. In *Figure 9B*, it is interesting to note that the major bradycardic effect is seen on going from control to 10 mg (bid). Further increases in dose above 10 mg result in only a small further drop in heart rate, indicating there appears to be a "plateau effect" such that the maximal drop in heart rate seen in this study plateaus at about 30%. This is in accordance with the in vitro and simulation data shown in *Figure 8*, suggesting that even complete block of I_f will not cause

Figure 8. Effects of inhibition of I_f on spontaneous action potentials from an SA node cell (A), and current recorded in a voltage-clamped sinoatrial (SA) node cell (B), and a computer model of the SA node action potential (C). A: Ivabradine ($0.3 \mu\text{M}$) slows the spontaneous rate of an isolated SA node cell by slowing the diastolic depolarization phase without affecting the shape of the subsequent action potential. B: Ivabradine ($3 \mu\text{M}$) blocks I_f in a voltage-clamped isolated SA node cell. C: Complete block of I_f in a computer-simulated model of the SA node action potential using the Cellular Open Resource program developed by Noble and colleagues⁴⁹ slows, but does not abolish, repetitive activity.

Redrawn from reference 22: Baruscotti M, DiFrancesco D. Pacemaker channels. *Ann N Y Acad Sci.* 2004;1015:111-121. Copyright © 2004, New York Academy of Sciences.

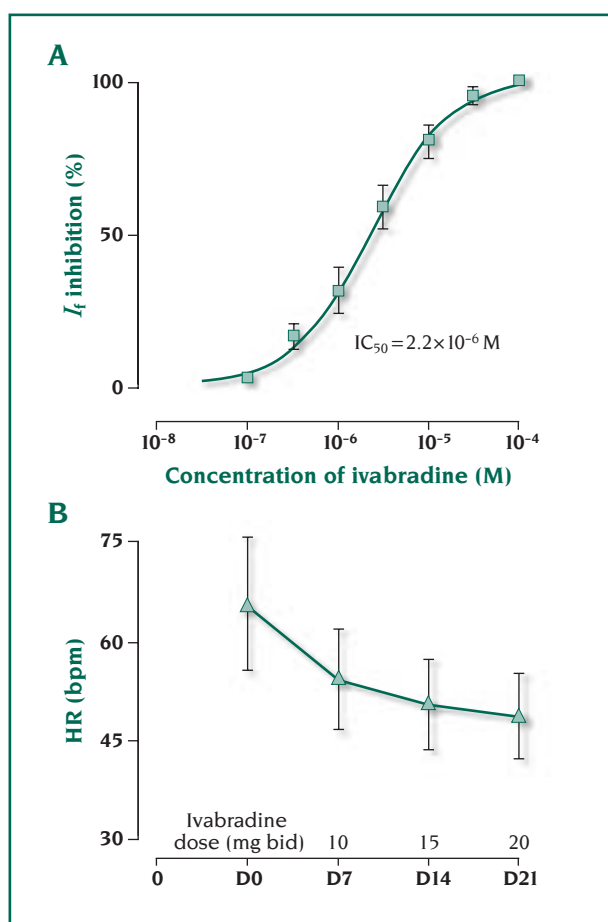


Figure 9. Dose-dependent effects of ivabradine on I_f (A) and heart rate (HR) (B). A: Dose-response curve for steady-state block of I_f measured in a rabbit sinoatrial node cell paced at 6 Hz with a 1.8 s voltage-clamp step from -30 mV to -100 mV . B: Effects of ivabradine on heart rate from a dose-titration study in which ivabradine concentration was incrementally increased every 7 days from control (0) to 20 mg (bid).

Panel A is redrawn from reference 27: Bois P, Bescond J, Renaudon B, Lenfant J. Mode of action of bradycardic agent, S 16257, on ionic currents of rabbit sinoatrial node cells. *Br J Pharmacol.* 1996;118:1051-1057. Copyright © 1996, Nature Publishing Group.

Panel B is based on reference 50: European Public Assessment Report. London, UK: EMEA; 2005:20.

A further fail-safe mechanism is provided by the dispersion of pacemaker cells within the SA node. The dissemination of anatomically and electrophysiologically defined pacemaker tissue within the region of the SA node is such that more than one site can function as the pacemaker, with the most rapid site of impulse initiation overdrive-suppressing the slower sites. Autonomic tone and other less-well defined interventions also influence both site and rate of cardiac pacemaking.

A problem that arises is in the setting of SA nodal dysfunction, where bradycardias and tachycardias may occur often in seemingly haphazard juxtaposition, although the initiation of tachycardia after a period of bradycardia has been well defined. Treatment is often difficult and may involve the use of SA nodal ablation and device therapy. One might question whether this syndrome, or family of syndromes, arises from a malfunction in the primary pacemaker current, I_f , or in one of the other currents that contribute to the pacemaker potential. Alternatively, does it come about as a result of structural abnormalities in the nodal region, such as excess uncoupling of pacemaker cells from one another and the surrounding tissues? These are issues for which there are currently no answers and which must be solved if we are to contend with this important cardiac rhythm disturbance.

severe bradycardia or sinus arrest. Thus, assuming ivabradine is indeed selective for the I_f channel, then, at least in terms of cardiotoxicity, this agent is likely to be safe and of potential therapeutic benefit in pathologies where lowering the heart rate is desirable.

CAN "FAIL-SAFE" GO TOO FAR? THE PLUSES AND MINUSES OF INTERACTIVE BACKUP SYSTEMS

As detailed above, one of the positive aspects of a pacemaker whose function is supported by multiple ion currents is that in the event of malfunction of part of the system, other limbs may come into play. For example, excess hyperpolarizing action of outward K currents may be counteracted by the activation of the inward I_f pacemaker current. The rapid rates that may be achieved with excess increases in net inward current or decreases in repolarizing current may be attenuated by enhanced vagal tone to decrease I_f and increase $I_{K,ACh}$. The latter current provides yet another means whereby hyperpolarization and a decrease in diastolic depolarization and pacemaker rate may be achieved.

CONCLUSION

In summary, the mammalian SA node is a complex heterogeneous mixture of nodal cells, atrial tissue, and connective tissue. The nodal cells themselves are both morphologically and electrophysiologically heterogeneous and it is this macro- and micro-diversity that is key to the functioning of the node. The heterogeneous ion channel expression in different regions of the node and the multiple ion channels within a single cell that contribute to pacemaker activity make the node fail-safe and very hard to stop. The multiple currents contributing to the pacemaker depolarization, and the high



input-impedance of the nodal cells, mean that not only is the node hard to stop, but it is also exquisitely regulatable. That is, small currents can exert significant effects on heart rate. One such small current that appears to play a crucial regulatory role is the hyperpolarization-activated cyclic nucleotide gated cation channel that conducts the "funny" current I_f . Prevailing evidence suggest that it is this current that is the target for both the adrenergic and cholinergic modulation of heart rate. I_f is also the target for a new class of specific bradycardic agents such as ivabradine that have the potential to safely and selectively lower heart rate without the inotropic consequences of other rate-slowing agents such as the β -blockers or Ca antagonists. The fail-safe nature of the node and the specificity of ivabradine suggest that this agent should be a safe and effective way of lowering heart rate without the risk of profound bradycardia or sinus arrest. Results of the BEAUT I_f UL trial (MorBidity-mortality Evaluation of the I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction), which concludes in December 2007, should shed more light on the clinical benefits expected from this promising agent.

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